Trace elements in uremia and hemodialysis[1]

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ABSTRACT Some of the toxic and nutritional aspects of trace elements in patients with renal failure are reviewed. Data are presented that tend to disprove the hypothesis that aluminum poisoning alone is responsible for dialysis encephalopathy. Possible dietary restrictions imposed in uremic patients may impair iron, zinc, copper, manganese, or chromium nutriture. *Am. J. Clin. Nutr.* 33: 1501–1508, 1980.

Trace elements are those elements that occur in the body in microgram per gram amounts or less. They function as cofactors for many enzymes, and in some instances, are part of the structure of nonenzyme proteins.

Fifteen trace elements have been reported to be either beneficial or essential for higher animals. Included are iron, zinc, copper, manganese, chromium, cobalt, selenium, iodine, fluorine, nickel, vanadium, arsenic, molybdenum, silicon, and tin. The first nine are either essential or beneficial for man. The roles of the latter six in human nutrition may be clarified during the next decade.

The major toxic elements in the environment are lead, mercury, and cadmium. Arsenic and thorium, are important to persons exposed but are not widespread in the environment.

Trace elements that seem potentially hazardous to uremic patients include all the above plus aluminum, lithium and strontium. Elements become hazardous when they either contaminate dialysis fluids or are present in diets at levels that exceed those which can be easily removed by dialysis. Fortunately, intoxication with any of these elements appears to be unusual.

Acute poisoning is probably rare. However, chronic toxicity, which is obscure in onset and occult in manifestations, may be a potential hazard if water supply or dialysis equipment is contaminated. It therefore seems likely that chronic toxicity, if it occurs, may be somewhat unique in terms of cause and severity to each dialysis center. At present, the practical importance of chronic toxicity from any of the trace elements is under investigation. Changes in the tissue content of trace elements of uremic patients who have been treated with or without dialysis have been described.

Alfrey and Smythe (1) reported the element content of tissues of 80 patients with uremia who had been treated with or without dialysis (**Table 1**). They measured iron, zinc, copper, selenium, rubidium and strontium in aorta, bone, brain, heart, kidney, liver, and muscle. The significant differences in trace element content are shown in Table 1. One of the most striking findings was a decrease in rubidium content of all tissues of patients. Dialysis apparently decreased the iron in heart and the zinc in muscle. Zinc was increased in the liver of all patients, but the increase was less in dialyzed than in nondialyzed patients.

Analysis of gray matter from dialyzed patients (**Table 2**) revealed highly significant elevations in the concentrations of molybdenum, aluminum, and iron, and significant elevations in calcium, strontium, and zinc (2). Arsenic, rubidium, and bromine displayed highly significant depressions, while copper, selenium, and lead were unchanged.

Uranium was elevated in tissues from a patient treated with hemodialysis. The water supply used for the dialysis contained uranium (3). Similarly contamination of the dialysate with nickel has been shown to cause an increase in patients' plasma, and has been associated with signs of acute intoxication that included headache, dizziness, nausea and vomiting (2). Hyperstannism has been ob-

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TABLE 1
Element content of tissues in uremia with or without dialysis[a] (1)

		Fe	Zn	Cu	Se	Rb	Sr
Aorta	C̄					↓[b]	↑[c]
	S̄					↓[b]	↑[c]
Bone	C̄					↓[c]	↑[b]
	S̄					↓[b]	↑[b]
Brain	C̄		↑[c]			↓[b]	
	S̄		↑[c]		↑[b]	↓[b]	
Heart	C̄	↓[b]	↑[c]			↓[b]	↑[c]
	S̄		↑[c]			↓[b]	
Kidney	C̄	↓[b]	↓[b]	↓[b]	↓[b]	↓[b]	↑[b]
	S̄	↓[b]	↓[b]	↓[b]	↓[b]	↓[b]	↑[b]
Liver	C̄		↑[c]			↓[b]	↑[b]
	S̄		↑[b]				
Muscle	C̄		↓[c]			↓[c]	
	S̄						

[a] n = 80. [b] $P < 0.01$. [c] $P < 0.05$.

TABLE 2
Element content of gray matter of dialyzed uremic patients (2)

Increased	Decreased	Unchanged
Ca[a]	As[b]	Cu
Sr[a]	Br[c]	Se
Mo[d]	Rb[d]	Pb
Al[d]		
Fe[b]		
Zn[a]		
n= 57		

[a] $P < 0.05$. [b] $P < 0.01$. [c] $P < 0.005$. [d] $P < 0.001$.

served both in dialyzed and nondialyzed uremic patients. The increases in tissue appear to have been sequelae of uremia and not of dialysis (4).

The above information indicates that marked changes in the trace element content of tissues are associated with uremia whether or not patients are treated with dialysis. The relationship of these abnormalities in tissue content of trace elements to illness is unclear. The controversy surrounding the hypothesis that dialysis encephalopathy is caused by chronic aluminum poisoning illustrates the current lack of understanding. The hypothesis is based in part on the finding of elevated concentrations of aluminum in brains of patients with certain degenerative dementias. In another paper of this symposium, data are presented that support the hypothesis. Therefore, findings that are not supportive are presented here.

Blood aluminum levels increase (**Fig. 1**) in patients who are dialyzed with water containing aluminum (5). The finding of an increase does not, however, prove that aluminum is harmful. The possibility that aluminum may be less toxic than the hypothesis suggests is supported by the finding that patients with acute or chronic renal failure, who had been treated with dialysis, had lower levels of aluminum in brain gray matter than patients who died of uremia without dialysis treatment (**Fig. 2**), (6). In addition, there was a wide variation in the levels of aluminum in gray matter from patients who displayed dialysis encephalopathy. Some of the values were similar to those of patients who had not had encephalopathy. It was also found that patients who died in hepatic coma had levels of aluminum in gray matter that were similar to those of patients who died of renal failure and had been treated with dialysis. When data from three published studies were compared by Arieff et al. (6), patients who had died with dialysis encephalopathy had a wide range of gray matter aluminum (**Fig. 3**). Some of the levels were similar to those of patients who had not had encephalopathy and died of chronic renal failure subsequent to treatment with or without dialysis. Comparison of the tissue concentrations of aluminum in these patients suggests that the levels of aluminum in brain gray matter may not, by themselves, account for the occurrence of dialysis encephalopathy. Some patients displayed encephalopathy when the levels of aluminum in gray

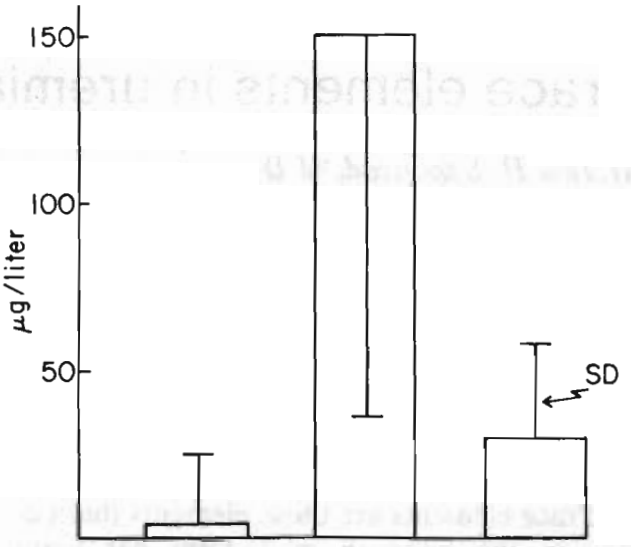

FIG. 1. Plasma aluminum levels before, immediately after, and 2 weeks after dialysis with water containing increased levels of aluminum (5).

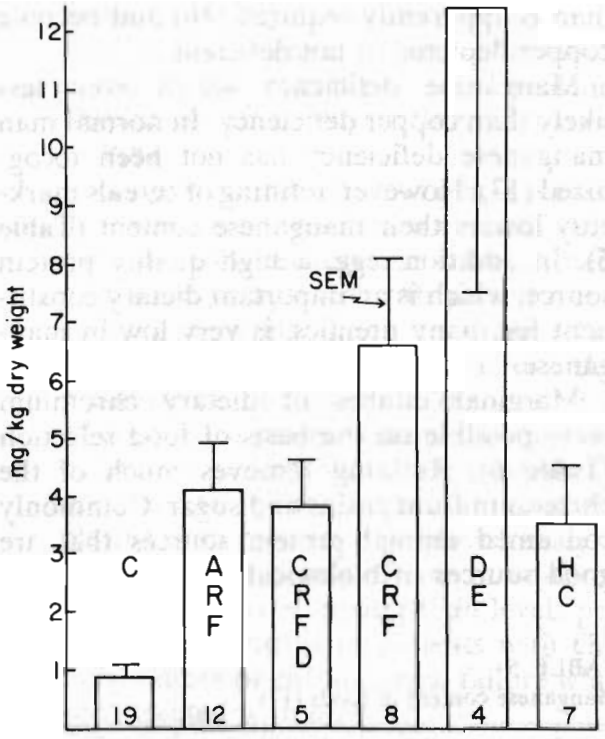

FIG. 2. Aluminum concentrations in gray matter of control (c) patients, patients with acute renal failure (ARF), chronic renal failure treated with dialysis (CRFD), chronic renal failure treated without dialysis (CRF), dialysis encephalopathy (DE), and hepatic coma (HC) (6). The SEM for each group is indicated.

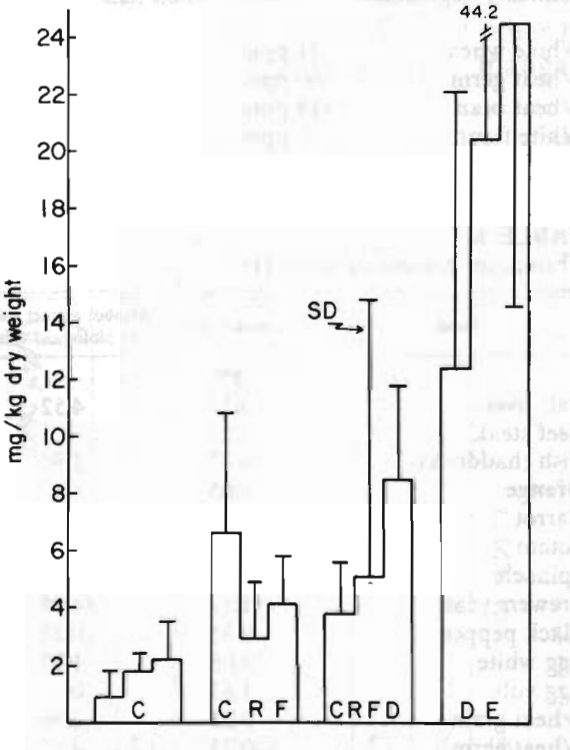

FIG. 3. Aluminum concentration in gray matter of patients in three studies. Control (c) levels are compared with those of patients with chronic renal failure (CRF), chronic renal failure treated with dialysis (CRFD) and dialysis encephalopathy (DE) (6). The SD for each group of observations is indicated.

matter were similar to levels found in renal failure patients without encephalopathy. In addition the occurrence of EEG abnormalities believed characteristic of dialysis encephalopathy did not seem related to the level of aluminum in gray matter. EEG abnormalities were found in patients with encephalopathy but not in patients with similar levels of gray matter aluminum and no encephalopathy (6). Data from experimental animals supported this interpretation of the findings from humans. If the observations of Arieff et al. (6) are correct it seems reasonable to conclude that a cause and effect relationship between aluminum and dialysis encephalopathy has not been established. If, however, excess aluminum in gray matter does contribute to the occurrence of encephalopathy in humans, the reasons for the clinical and experimental disparities, which do not support the hypothesis, should be explained.

In contrast to toxicities, trace element deficiencies are a potential problem for all patients with renal failure. The trace elements most likely to be deficient are iron, zinc, copper, chromium, and manganese. Dietary lack is likely to be a major factor if patients are maintained on diets low in meat, and high in refined foods such as pasta, sucrose and oils. Blood loss from gastrointestinal bleeding may be a contributing factor, especially in iron deficiency.

Iron deficiency in uremic patients is caused not only by low dietary levels, but by the chemical form of the iron. The most easily absorbed form of food iron is heme iron. Up to 35% may be absorbed by iron-deficient individuals. Heme iron is present in meat and, in contrast, nonheme iron that is present in plants is much less well absorbed (7). Iron absorption may also be impaired by the phytate and dietary fiber in foods of vegetable origin (8, 9). These components can form insoluble complexes with iron in the alkaline environment of the intestinal lumen. Liberal intakes of foods containing dietary fiber or phytate may significantly impair iron homeostasis, particularly, if the diet is not rich in readily available iron.

The adequacy of dietary zinc depends both on the amount, and its availability for absorption. Seafood and meat are the best sources (**Table 3**) (10); in comparison cereals are inferior, the levels of zinc are lower and

the presence of dietary fiber and phytate may interfere with zinc absorption (9, 11). Refining of grains, which removes most of the fiber and phytate, also removes much of the zinc. Fruits and vegetables, vegetable oils, and refined sugar are generally very poor sources of zinc. Thus, it seems that dietary zinc deficiency would be most likely in patients whose intakes of animal protein, particularly meat, are severely restricted. This was apparently observed by Mansouri et al. (12).

Copper deficiency seems less likely than zinc or iron deficiency. In nonuremic individuals copper deficiency is rare (13) and nonnephrotic patients have been observed to have normal (12) or increased (14) blood levels of copper. On the other hand the nephrotic syndrome can result in marked losses of copper and hypocupremia (15). A low dietary intake of copper seems possible, however, because good sources of copper (**Table 4**) may be excluded from the diets of some patients. Refining decreases the level of copper in flour and other foods. These factors, together, appear to increase the likelihood that uremic patients may consume less copper than is apparently required (16) and become copper depleted, if not deficient.

Manganese deficiency seems even less likely than copper deficiency. In normal man manganese deficiency has not been recognized (17). However, refining of cereals markedly lowers their manganese content (**Table 5**). In addition, egg, a high quality protein source, which is an important dietary constituent for many uremics, is very low in manganese.

Marginal intakes of dietary chromium seem possible on the basis of food selection (**Table 6**). Refining removes much of the chromium from grains and sugar. Commonly consumed animal protein sources that are good sources of biologically active, alcohol-

TABLE 3
Zinc content of foods (10)

Food	Concentration
	ppm
Oyster	1000
Other sea food	
Muscle meat	30–50
Nuts	
Hard wheat	25
Soft wheat	20
Patent flour	6
Patent soft flour	4
White sugar	<1
Citrus fruits	
Nonleafy vegetables	
Tubers	
Vegetable oils	

TABLE 4
Copper content of foods (13)

Good sources	Poor sources
100 μg/100 kcal	*50 μg/100 kcal*
Oyster	Cheese
Fish	Milk
Organ meats	Beef
Legumes	White/brown bread
Nuts	Breakfast cereals
Green vegetables	

TABLE 5
Manganese content of foods (17)

Good sources	Poor sources
20–30 ppm	*0.2–0.5 ppm*
Nuts	Animal tissue
Whole cereals	Milk and cheese
Dried fruits	Poultry
Roots and tubers	Eggs
Fruits	Fish
Nonleafy vegetables	Shell fish

Whole wheat	31 ppm
Wheat germ	160 ppm
Wheat bran	119 ppm
White flour	5 ppm

TABLE 6
Chromium content of foods (18)

Food	Concentration	Alcohol extract relative biological value
	ppm	
Calf liver	0.55	4.52
Beef steak	0.57	
Fish (haddock)	0.07	1.86
Orange	0.05	
Carrot	0.09	
Potato	0.21	
Spinach	0.10	
Brewers yeast	1.12	44.88
Black pepper	0.35	10.21
Egg white	0.08	1.77
Egg yolk	1.83	0
Wheat grain	0.28	2.96
Wheat germ	0.23	4.05
Wheat bran	0.38	2.21
Patent wheat flour	0.23	1.86
White bread	0.26	2.99
Whole wheat bread	0.42	3.59
Spaghetti	0.15	2.86

extractable chromium may be restricted in the diets of uremic patients. It should be noted, however, that published evidence for chromium deficiency in uremic patients is lacking.

In most patients dialysis per se is probably an unlikely cause of trace element deficiencies, possibly because the trace elements in blood are complexed with proteins and the cellular elements. Thus, they are relatively unavailable for movement across dialysis membranes. For example, the lack of effect of dialysis on plasma zinc is shown in **Figure 4**. Uremic patients who were treated without dialysis had lower concentrations of zinc in plasma than patients treated with dialysis. At the same time, levels of zinc in erythrocytes were similar to or greater than levels present in normal controls in patients with chronic renal failure or chronic renal failure who had been treated with dialysis.

The diagnosis of trace element deficiencies requires an awareness of their potential occurrence, the capability for analytical measurement, and a knowledge of the signs and symptoms that may be associated with deficiencies. The criteria and methodology for assessing iron status (7) are widely known and will not be reviewed. On the other hand, characteristics of zinc, copper, manganese, and chromium deficiencies are not well known and will therefore be briefly summarized.

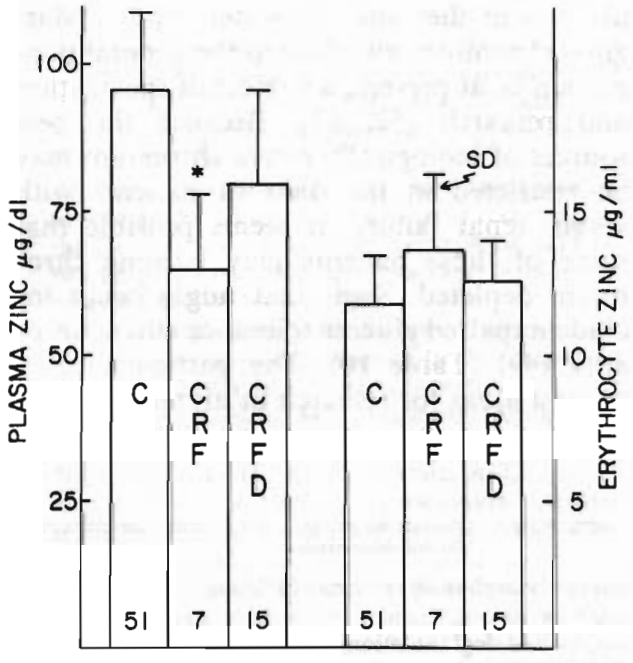

FIG. 4. Plasma and erythrocyte zinc levels of patients with chronic renal failure (CRF) and chronic renal failure treated with dialysis (CRFD) compared to controls (c). SD for the groups are indicated.

Zinc deficiency has been observed both as a primary and secondary illness. Dietary deficiency in humans was first characterized in 1963 (19, 20). The response to zinc therapy was reported in 1967 (21). Since then, conditioned (22–25) and primary (dietary) deficiencies (26–31) have been observed in a variety of clinical settings. Estimates of human requirements for zinc have been published (16, 32, 33).

Some of the signs and symptoms that have been associated with zinc deficiency and abnormalities, which may be related, are listed in **Table 7**. The abnormalities associated with zinc deficiency have been studied in detail in animals (10, 24). Recognition of their occurrence in man has been directly related to knowledge obtained from these basic studies. It was previously noted that zinc deficiency probably should not be attributed to dialysis per se. Two studies, however, suggest that this may not always be true. Patients suffering from impotence subsequent to initiation of dialysis were relieved of symptoms subsequent to zinc administration (34). In the other study, hypogeusia and anorexia were improved and caloric intake increased subsequent to zinc treatment (35). Thus it seems possible that plasma and erythrocyte levels of zinc may not give a true indication of the zinc nutriture of tissues of patients with uremia. This suggestion is consistent with observations in nonuremic persons (25).

TABLE 7
Signs of zinc deficiency

Sign/symptom	Related abnormalities
Acne/rash/infections	Impaired cell-mediated immunity
Impotence	Decreased pituitary gonadotropin
Testicular atrophy	
Delayed healing	Impaired collagen formation
Hair loss	Atrophy of hair follicles
Poor utilization of protein	Decreased synthesis of DNA, RNA, protein
Decreased central nervous system function	Abnormal tryptophane and tyrosine metabolism (in rats)
Ataxia	
Depression	
Impaired taste acuity	
Anorexia	

Copper deficiency has been recognized far less frequently in humans than zinc deficiency (13). Most instances have been described in infants fed exclusively on milk or milk-based formulas low in copper (36, 37), infants with Menke's syndrome (38), and patients receiving total parenteral alimentation (39, 40). The signs of copper deficiency (**Table 8**) are easily produced in animals. Not all have been described in humans. Leukopenia, hypochromic microcytic anemia, and osteopenia occur in humans (36). Apparently, infants with Menke's syndrome may develop aneurysmal dilatations of small arteries (38). Severe diarrhea (41) and myocardiopathy (41, 42) occur in copper-deficient cattle, while myocardiopathy, abnormal arterial collagen and elastin formation (43) and hypercholesterolemia (44) occur in copper-deprived rats, as well as other species (13). In animals, copper deficiency can be produced not only by a diet low in copper, but by interference of certain other trace elements with copper-dependent metabolic processes. These elements include cadmium, zinc, and molybdenum (13). The antagonistic effects of these elements on the copper metabolism of animals suggest that patients with low or marginal intakes of copper may have an increased risk of copper deficiency, if they are exposed to elevated levels of cadmium, zinc, or molybdenum. In support of this suggestion is the toxic interaction between zinc and copper that was observed in patients with sickle cell disease who were treated with 150 mg of zinc daily (45), a level 10 times the Recommended Dietary Allowance (46).

While manganese deficiency can be produced in experimental animals with relative ease (17), its natural occurrence in man has not been described. One possible instance of manganese deficiency was observed in a volunteer who was fed a formula diet that accidentally did not contain adequate manganese (47). Signs of manganese deficiency and related abnormalities, in animals are shown in **Table 9**. The effects on mucopolysaccharide metabolism and osteogenesis (17), and on the beta cells of the islets of Langerhans (48) may suggest areas for research because it seems possible that the peculiarities of diets fed uremic patients might contribute to manganese depletion in some.

Chromium deficiency has been observed in humans under special circumstances, such as long-term, total parenteral alimentation at home (49), and in some infants and children with severe protein-calorie malnutrition (50, 51). In the children the deficiency apparently was related to the level of chromium in the indigenous diet and the water supply. Marginal chromium nutriture in the general population is, at present, a subject of speculation and research (52, 53). Because the best sources of biologically active chromium may be restricted in the diets of patients with severe renal failure, it seems possible that some of these patients may become chromium depleted. Signs that might occur include impaired glucose tolerance and neuropathy (49) (**Table 10**). The particular signs suggest areas for research in uremia.

TABLE 8
Signs of copper deficiency

Signs/symptoms	Related abnormalities
Leukopenia	
Anemia	Impaired iron utilization
Fractures	Osteopenia
Arterial aneurysm	Impaired collagen and elastin synthesis
Cardiac arrhythmia	Heart muscle necrosis
Sudden death	
Hypercholesterolemia	Increased cholesterol synthesis
Diarrhea	Atrophy intestinal mucosa

TABLE 9
Signs of manganese deficiency

Signs/symptoms	Related abnormalities
Skeletal abnormalities	Impaired mucopolysaccharide synthesis cartilage
Impaired spatial orientation	Abnormal otoliths
Glucose intolerance	Beta cell atrophy and degranulation
Decreased serum cholesterol	Impaired cholesterol synthesis
Bleeding	Impaired prothrombin synthesis
Decreased metabolic rate	Ultrastructural abnormalities in mitochondria and endoplasmic reticulum

TABLE 10
Signs of chromium deficiency

Signs/symptoms	Related abnormalities
Hyperglycemia	Decreased insulin effectiveness
Growth failure	Decreased amino acid use
Neuropathy	
Cataract	
Atherosclerosis	Increased serum cholesterol

Summary

Trace elements are potentially important, both toxicologically and nutritionally, in patients with uremia. Present knowledge of the contribution of trace element toxicity or deficiency to syndromes observed in uremic individuals is limited. Tissue accumulation and loss of specific trace elements have been documented. The hypothesis that aluminum toxicity is the cause of dialysis encephalopathy does not appear to be true. The trace elements that seem most likely to become deficient in uremic patients are iron, zinc, copper, manganese and chromium. Examples of uremic, hemodialyzed patients with zinc-responsive hypogeusia and impotence have been described. Analogous examples consistent with copper, manganese or chromium deficiencies have not been recognized in association with uremia.

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